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Cognitive dysfunction and dementia in Parkinson's disease

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Summary. Parkinson's disease (PD) is a slowly progressive neurodegenerative disorder mainly characterized by degeneration of dopaminergic neurons in the substantia nigra and the ventral tegmental area, in combination with a varying loss of central noradrenergic (locus coeruleus), cholinergic (nucleus basalis of Meynert) and serotonergic (dorsal raphe nuclei) integrity, leading to a multitude of motor and non-motor behavioral disturbances.

Apart from the clinical motor hallmarks, in the early stages of disease, subtle cognitive dysfunction might be seen comprising mainly executive dysfunction, with secondary visuospatial and mnemonic disturbances. In about 20–40% of patients, these problems may eventually proceed to dementia, which constitutes an important risk factor for caregiver distress, decreased quality of life and nursing home placement. Dementia in PD is typically characterized by a progressive dysexecutive syndrome with attentional deficits and fluctuating cognition, often accompanied by psychotic symptoms. It is thought to be the result of a combination of both subcortical and cortical changes. PD-related dopaminergic deficiency in the nucleus caudatus and mesocortical areas (due to degeneration of projections from the substantia nigra and ventral tegmental area) and cholinergic deficiency in the cortex (due to degeneration of ascending projections from the nucleus basalis of Meynert), combined with additional Alzheimer-pathology and cortical Lewy bodies, may greatly contribute to dementia.

Current treatment of dementia in PD is based on compensation of the profound cholinergic deficiency. Recent studies with the cholinesterase inhibitors galantamine, donepezil and rivastigmine show promising results in improving cognition and ameliorating psychotic symptoms, which must further be confirmed in randomized controlled trials.

Keywords: Parkinson's disease, cognition, dementia.

Introduction

Parkinson's disease is a slowly progressive neurodegenerative disease, in which dopaminergic neurons in the substantia nigra and the ventral tegmental area degenerate, leading to dopaminergic deficiency in the striatum and mesocorticolimbic areas. In addition to degeneration of the dopaminergic system, in PD other ascending subcortical neurotransmitter systems are affected as well: the cholinergic system (nucleus basalis of Meynert), the noradrenergic system (locus coeruleus) and serotonergic system (dorsal raphe nuclei) (Jellinger, 1999). The cardinal motor symptoms are brady(hypo-)kinesia, tremor, rigidity and postural instability. Non-motor symptoms mainly comprise autonomic disturbances, depression, cognitive dysfunction/dementia and psychotic symptoms. As a rule, these symptoms are often more important in determining the quality of life of patients and caregivers than the motor disturbances.

Dementia in PD constitutes not only an important factor for caregiver distress and nursing home placement (Aarsland, 2000, 1999), but is also associated with increased mortality (independent of severity of motor symptoms) (Levy, 2000). As these symptoms are potentially treatable, identification is of major clinical importance both for the patients and their caregivers and may enable the Parkinson's disease patient to maintain living at home for a longer period. Additionally, postponement of nursing home placement can lead to substantial reductions in healthcare costs.

Cognitive deficits in non-demented PD patients

Cognitive impairment is often associated with PD, although deficits may be relatively subtle and not clinically apparent, or not overtly affect daily functioning. However, when compared to controls, subtle to prominent cognitive impairment is almost always found in PD patients. A wide variety of cognitive deficits has been described in non-demented PD patients, the most prominent of which is a deficit in executive function.

Executive function is a broad term used to describe a range of cognitive functions involved in the realisations of goal-directed, adaptive behaviour in response to new, challenging environmental situations, including attention, inhibition, task management, planning, monitoring and coding (Smith, 1999). A dysexecutive syndrome, resembling cognitive deficits found in frontal lobe patients (Rowe, 2002; Rogers, 1998a), is thought to be at the heart of cognitive dysfunction and dementia in PD and is usually one of the earliest cognitive symptoms found in PD (Dubois, 1997).

Besides executive dysfunction, there is considerable evidence of deficits in *visuospatial function* in non-demented PD, even when tests contain few motor components (Hovestadt, 1987; Boller, 1984; Bowen, 1972). Most authors, however, believe visuospatial dysfunction to be the result of the high cognitive demand that is usually required by such tasks. Indeed, with the possible exception of judgment of line orientation, it would appear that visuospatial dysfunction in PD can be readily explained by the demand of visuospatial tasks on executive functions such as planning and (shifting of) attention (Bondi, 1993; Raskin, 1992; Ogden, 1990; Ransmayr, 1987; Brown, 1986).

Mnemonic dysfunction has also frequently been reported in PD. The most consistent findings in patients with PD are deficits of working memory (Owen, 1993; Cooper, 1993, 1992; Bradley, 1989; Wilson, 1980) and explicit memory (Buytenhuijs, 1994; Taylor, 1990, 1986). Working memory can be defined as the ability to hold internal representations in short-term memory and to manipulate this mnemonic information on line to enable adaptive behaviour to be based on these representations rather than on immediate stimuli (Goldman-Rakic, 1987). Most studies find preserved short-term memory in non-demented PD (Owen, 1997). The executive processes that operate on the contents of this memory, however, are often impaired (Pillon, 1998). Therefore, most deficits in working memory can probably also be explained in terms of executive dysfunction. Defective explicit memory in PD can largely be remedied by semantic cueing or probing (Scheltens, 1999; Pillon, 1993). This suggests that although new information is stored, it is not readily accessed, pointing to defective usage of stored information. In conclusion, quite analogous to visuospatial function, mnemonic function would for the most part be secondarily impaired, due to the reliance of its manifestation on executive functionality.

Several studies have also shown bradyphrenia in PD (Cooper, 1994; Mayeux, 1987), although this is still a matter of much controversy in the literature. It has been suggested that the finding of reduced cognitive speed may very well have been caused by the inclusion of patients with mild dementia or depression (Smith, 1998). For an excellent and comprehensive review of the literature on cognitive deficits in PD, one is advised to read the chapter by Pillon and co-workers in the recent Handbook of Neuropsychology (Pillon, 2001).

Dementia in PD

The aforementioned cognitive deficits may eventually proceed to dementia in a number of patients. Prevalence and incidence vary considerably among studies, possibly due to differences in patient population, study design and criteria for diagnosing PD and dementia. In cross-sectional studies, prevalence of dementia in PD ranges from 10% to over 40% (Aarsland, 1996; Mayeux, 1988, 1992). Features associated with prevalence of dementia include age (Aarsland, 1996; Mayeux, 1988), age at onset of PD (Aarsland, 1996; Mayeux, 1988, 1992), disease severity (Mayeux, 1988), disease duration (Aarsland, 1996), depression (Aarsland, 1996) and presence of atypical parkinsonian symptoms (Aarsland, 1996). The association with older age is of particular strength.

Prospective studies have reported a cumulative incidence of 19 to 53% (the follow up period varied in these studies) (Read, 2001; Levy, 2000; Hughes, 2000; Marder, 1995). Recently, in a prospective study with 8 years follow-up, 78.2% of patients eventually developed dementia (Aarsland, 2003a). Incidence rates vary from 31.4 to 122.5 cases per 1000 person years (Aarsland, 1996, 2003a; Read, 2001; Hughes, 2000; Mahieux, 1998; Mayeux, 1990) and the risk for developing dementia in PD-patients is up to six times higher compared to age-matched control subjects (Aarsland, 2001).

In these studies, factors associated with the risk of dementia were found to be age (Levy, 2002; Aarsland, 2001; Read, 2001; Stern, 1993), age at onset of PD (Mahieux, 1998), disease severity (Aarsland, 2001; Hughes, 2000; Marder, 1995; Elizan, 1986), age at entry in the study (Read, 2001; Hughes, 2000), confusional state (Stern, 1993; Elizan, 1986), early hallucinations and the mixed tremor/akinetic form of PD (Aarsland, 2003a).

The neuropsychological profile of PD-related dementia is characterized by a progressive dysexecutive syndrome, as described earlier. Essentially, the same types of deficits are found in non-demented patients (Girotti, 1988), but are more severe in demented patients. From this perspective, it is not surprising that several recent studies have pointed to the predictive value of prodromal impairment of verbal memory (immediate and delayed recall) and especially executive function (Woods, 2003; Levy, 2002; Jacobs, 1995).

Memory deficits are present, but are less severe compared to AD (Aarsland, 2003c). Moreover, the quality of memory impairment differs from that seen in AD. In both conditions it is characterized by a deficit in free recall, but in PDD, as mentioned before, this can often be corrected by semantic cueing (Scheltens, 1999). Therefore, in PDD the problem seems to be of retrieval, and not of encoding. Indeed, recognition memory is often well preserved in demented PD-patients.

Unlike in AD, instrumental disorders such as aphasia, apraxia or agnosia are not very common in PDD (Dubois, 1997; Huber, 1989).

Psychotic symptoms however, are especially common in PDD. Hallucinations (sensory percepts in the absence of an external stimulus (American Psychiatric Association, 1994)), mainly visual, are the most frequent symptom. These are mostly non-threatening and often consist of vivid, colourful and sometimes fragmented figures of beloved (deceased) familiar persons and/or animals, which are described in detail (Poewe, 2003). Insight is retained in the majority of occasions, but with reality testing deteriorating, the hallucinations may change and become more frightening, possibly inducing anxiety and panic attacks (Wolters, 2001). Loss of insight is particularly seen in demented patients (Fenelon, 2000). Delusions (false beliefs based on incorrect inference about external reality (American Psychiatric Association, 1994)) are less common than hallucinations and mainly of the paranoid type, dealing with persecution, spousal infidelity or jealousy (Bosboom, 2004).

Attentional deficits and fluctuating cognition are also very common in PDD. These features, together with parkinsonism and the above mentioned visual hallucinations, are the main characteristics of dementia with Lewy bodies (DLB), possibly accounting for 15–20% of the dementias (McKeith, 1996). Indeed, PDD and DLB share many clinical (Ballard, 2002; Connor, 1998; Dubois, 1997) and pathological (Harding, 2001) features and are often difficult to distinguish other than by the temporary onset of dementia and psychosis in relation to parkinsonism (Richard, 2002). Therefore, Parkinson's disease and dementia with Lewy bodies are often considered to be part of the same disease spectrum (Burn, 2003a; Ballard, 2000; McKeith, 2000b), although this matter is still under considerable debate (Litvan, 1998). It is suggested that similar pathological mechanisms may underlie the clinical symptoms, including dementia and psychotic symptoms.

Pathophysiology of cognitive deficits and dementia in PD

Based on his work in primates, Alexander described five parallel, segregated circuits interconnecting well-defined subregions of the basal ganglia to particular cortical fields via the thalamus (Alexander, 1986). Disruptions at either basal ganglia or cortical points in such a circuit have been shown to produce similar behavioural effects (Cummings, 1993). In one of the five circuits, the so-called dorsolateral prefrontal loop which is thought to be involved in executive behaviour, the dorsolateral part of the prefrontal cortex projects to the caudate nucleus. Hence projections lead through pallidum and thalamus back to the prefrontal cortex. It may therefore well be that degeneration of the dopaminergic nigrostriatal pathway affects executive function by causing a disruption at the level of the caudate nucleus, a notion supported by findings from imaging studies (Lewis, 2004; Owen, 1998). This notion is further underlined by the fact that dopamine depletion in PD is greatest in the caudate's most rostral portion, exactly the part that is most heavily interconnected to the dorsolateral region of the prefrontal cortex.

Alternatively, cognitive dysfunction in non-demented PD could be caused by dopamine depletion in the frontal cortex itself, resulting from degeneration of the mesocortical dopaminergic system mainly projecting from the ventral tegmental area. In any case, the exact contribution of dopaminergic deficiency to cognitive defects in Parkinson's disease remains controversial, largely because the cognitive effects of dopaminomimetics appear heterogeneous. While some studies point to a positive effect on executive function (Lange, 1992, 1995), (working)memory and attention (Bowen, 1975), others actually find deleterious effects, especially in the executive domain (Gotham, 1988) or show no effects at all. A recent longitudinal study showed the beneficial effect of dopaminergic medication to be particularly prominent in the very early stages of disease (Kulisevsky, 2000b) (for a review of the pertinent literature, read (Kulisevsky et al., 2000a)). Also, cognitive function in PD seems to correlate with motor symptoms that show little response to dopaminergic treatment (axial symptoms and gait disturbances), but not with levodopa-responsive symptoms (akinesia and rigidity) (Burn, 2003b; Levy, 2000; Pillon, 1989).

In conclusion, it would appear that dopaminergic medication improves or impairs cognitive performance depending on both the nature of the task and the basal level of DA function in underlying nigrostriatal and mesocortical circuitry.

The exact pathophysiology of dementia in PD is uncertain. A number of neuropathological and neurochemical changes in PD are thought to be involved.

The aforementioned deterioration of the dopaminergic system is likely to contribute to the progression of cognitive deficits into more overt dementia. This is supported by the association between dementia and the loss of dopaminergic neurons in the medial part of the substantia nigra (Paulus, 1991; Rinne, 1989), projecting to the nucleus caudatus and mesocortical and mesolimbic areas, and in the ventral tegmental area, with ascending dopaminergic projections to mesocortical and mesolimbic areas (Oades, 1987; Thierry, 1978).

Still, dopaminergic deficiency by itself is not considered sufficient for the development of dementia. Non-dopaminergic systems are likely to be involved as well. As already mentioned, several neuromodulatory systems are affected to varying degree in PD, mainly the serotonergic, noradrenergic and cholinergic systems (Jellinger, 1999).

Neuronal loss in locus coeruleus (LC) and noradrenergic deficiency in the cortex were reported to be associated with dementia in PD (Cash, 1987). However, in other studies, this relationship could not be found (Paulus, 1991; Chan-Palay, 1989). Loss of serotonergic neurons in the dorsal raphe nucleus (DRN) has mainly been associated with depression, but demented and non-demented patients did not differ on neuronal counts in this area (Paulus, 1991; Scatton, 1983).

Furthermore, Perry et al. (1991) could not establish a correlation between dementia in PD and diminished monoaminergic activity. Instead, they reported an association between cholinergic deficiency and dementia. Indeed, not only in Alzheimer's disease (Francis, 1999; Davies, 1976), but especially in PDD and DLB, a cholinergic deficit has been implicated in the pathophysiology of cognitive impairment. In these patients, a definite and more pronounced depletion of cholinergic neurons is found in the nucleus basalis of Meynert compared to AD-patients and non-demented patients (Perry, 1985; Whitehouse, 1983), together with diminished cholinergic activity in the cortex (Ballard, 2002; Mattila, 2001; Tiraboschi, 2000; Perry, 1991). This nucleus in the basal forebrain, consisting for 90% of cholinergic neurons, provides major cholinergic projections to the amygdale and neocortex (Perry, 1985; Whitehouse, 1983; Mesulam, 1983a, b). The cholinergic deficit, possibly superposed on a normal age-related deterioration of the cholinergic system (Perry, 1992), is strongly correlated with cognitive impairment in both conditions (Mattila, 2001; Kuhl, 1996; Perry, 1985) and therefore, is likely to constitute an important mechanism in the development of dementia.

This is further supported by the propensity of anticholinergic agents to elicit cognitive dysfunction in PD-patients (Bedard, 1999; de Smet, 1982) and the clinical beneficial results of cholinesterase inhibitors in disorders with associated dementia (see later).

Beside these subcortical neuropathological changes in PDD, important cortical changes have been implicated in the etiology of dementia in PD. AD-pathology, especially AD-neurites, are more abundant in demented patients compared to non-demented PD-patients, correlating with the severity of PDD in a number of studies (Jellinger, 2002; de Vos, 1995), though other authors point to the importance of cortical LB's as a neuropathological substrate for dementia in PD (Apaydin, 2002; Harding, 2001; Hurtig, 2000; Mattila, 2000), independent of AD-pathology (Hurtig, 2000; Mattila, 1998, 2000). This, however, is opposed by authors reporting comparable cortical LB distribution in demented and non-demented PD-patients (Richard, 2002; SantaCruz, 1999; de Vos, 1995). Thus, this matter is still under considerable debate.

Overall, dementia in PD is thought to be the result of a combination of several subcortical and cortical pathological changes. Subcortical mechanisms include both dopaminergic deficiency in the nucleus caudatus and mesocortical

areas, causing executive dysfunction, and cortical cholinergic deficiency, mainly due to degeneration of the nucleus basalis of Meynert. The latter may further deteriorate the patient's executive functions by inducing attentional deficits (possibly together with noradrenergic deficiency). This effect might be increased by ageing. Additional AD-like changes and the presence of Lewy bodies in the cortex are likely to further compromise cognitive functions, with development of dementia as soon as a certain threshold is reached (Wolters, 1998).

Treatment of dementia in PD

Current pharmacological intervention in dementia is symptomatic and is based on compensation for the profound loss of cholinergic activity in the cortex. In AD, modest beneficial results have been reported with the cholinesterase inhibitors galantamine, rivastigmine and donepezil (Gabelli, 2003; Tariot, 2000; Cummings, 1998; Rogers, 1998b). These compounds might even prove to be more effective in PDD (and DLB) for several reasons. First, as mentioned above, the deterioration of ascending cholinergic projections from the nucleus basalis of Meynert is probably more pronounced in PDD and DLB compared to AD (Perry, 1985; Whitehouse, 1983). Second, the cortex is thought to be relatively spared in PDD (Perry, 1993).

An early study with tacrine in PD reported a definite amelioration of psychotic behaviour (Hutchinson, 1996), but this compound has been withdrawn from the market because of hepatotoxicity.

Galantamine and donepezil are cholinesterase inhibitors that stimulate the nicotinic receptor (Samochocki, 2000). In open label studies with these compounds, cognition as well as hallucinations improved in PD-patients with dementia without significant worsening of extrapyramidal features (Aarsland, 2003b; Bergman, 2002; Fabbrini, 2002; Werber, 2001).

Open label studies with rivastigmine, a dual acetyl and butyryl cholinesterase inhibitor have yielded similar results in PDD as well as DLB (Giladi, 2003; Bullock, 2002; Grace, 2001; Reading, 2001; McKeith, 2000a, c). In these studies, extrapyramidal features did not worsen significantly and even tended to improve in one (Reading, 2001) and worsened after withdrawal of rivastigmine in another (McKeith, 2000c). Given the possible parkinsonism inducing effects of cholinergic drugs, the improvement as seen in the motor scores of the Parkinson's disease patients treated with cholinesterase inhibitors is unexpected. In our own (unpublished) experience rivastigmine only tends to increase tremor in demented PD-patients.

The only randomized controlled trial with cholinesterase inhibitors in PDD so far, has been conducted with donepezil. The same beneficial results as in the previous open label studies have been reported, though the number of patients was small (Aarsland, 2002). A large, randomized, placebo controlled trial with rivastigmine in PDD, is currently being conducted.

The most frequent side effects reported with the use of cholinesterase inhibitors are nausea, vomiting and anorexia, sometimes causing problems with drug titration. Therefore, the drugs should be started at low dose with a gradual increase to the maximum tolerated dose.

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